Candidaemia in a European Paediatric University Hospital: a 10-year observational study

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Abstract

In this retrospective observational study covering 1998 to 2008, 32 patients (mean age: 7.50 years) were identified that had 35 episodes of candidaemia (0.47 cases/1000 hospital discharges). Cancer/allogeneic haematopoietic stem cell transplantation (43%) and congenital malformations/syndromes (21%) were the predominant underlying conditions. Central venous catheterization (90%), a history of antibacterial therapy (69%) and previous bacteraemia (54%) were frequent comorbidities. *Candida albicans* (46%) was most common, followed by *Candida parapsilosis* (17%) and *Candida glabrata* (14%). Resistance was infrequent and limited to non-albicans *Candida* spp. The 30-day and 100-day mortality rates were 11.4%.

Keywords: Candidaemia, paediatrics, epidemiology, mortality, mycoses, risk factors, treatment.

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Bloodstream infections by *Candida* spp. are an important cause of infectious morbidity and mortality in hospitalized patients [1]. Although there are several important investigations on the epidemiology of paediatric and neonatal candidaemia from the USA [2–9], comparable studies from Europe are restricted to Mediterranean countries [10–12]. We therefore analysed the incidence, demographic features and outcome of bloodstream infections due to *Candida* spp. among patients admitted to a German Paediatric University Hospital.

The study was a single-centre, retrospective observational cohort analysis covering the period from August 1998 to July 2008. The University Children's Hospital is an academic tertiary-care hospital and serves a population of *c.* 2.6 million residents. It consists of four departments (Paediatrics, Cardiology, Haematology/Oncology, Surgery) with *c.* 140 beds and 7500 hospital admissions/year. It has a 17-bed interdisciplinary intensive-care unit (ICU) with *c.* 650 admissions/year, and a haematopoietic stem cell transplantation (HSCT) programme with *c.* 20 allogeneic transplants/year. Patients eligible for inclusion had to have an episode of candidaemia, defined as the isolation of a *Candida* spp. from one or more blood cultures. Cases were identified through review of the Medical Microbiology records, and microbiological and clinical data were captured by a pseudonymized standardized case report form. Study design and data handling were reviewed and approved by the local ethics committee. Blood cultures were performed using BACTEC Peds Plus/F culture vials and the BACTEC 9240 system (Becton Dickinson, Paramus, NJ, USA). Yeast pathogens were sub-cultured on Sabouraud dextrose agar, processed for identification by micromorphology, fermentation and the API C32 identification system (BioMérieux, St Louis, France), and frozen at –70°C. For susceptibility testing, isolates were freshly sub-cultured and analysed as batch using a broth microdilution method as outlined in Table 2 [13–15].

During the 10-year period, 35 episodes of *Candida* bloodstream infections in 32 paediatric patients were identified; three patients (9%) had two separate episodes of candidaemia. The pooled average annual incidence was 0.47 cases/1000 hospital discharges (95% CI, 0.26–0.57) and 0.06 cases/1000 inpatient-days (95% CI, 0.035–0.073) without trend over time. The incidence was higher in oncology/HSCT patients (1.25; 95% CI, 0.74–1.57) compared with ICU patients (0.59; 95% CI, 0.02–1.09) and cardiology patients (0.51; 95% CI, –0.07 to 0.95), patients admitted to other paediatric wards (0.28; 95% CI, 0.00–0.52) and to paediatric surgery (0.18/1000 discharges; 95% CI, –0.08 to 0.42), respectively. Candidaemia was infrequent in neonates with three cases per 3977 hospital discharges (0.75 cases per

1000 hospital discharges (95% CI, –0.11 to 1.65); 1.08 in ≤36th week of gestation versus 0.46 in >36th week of gestation; 5.9 in <1000 g (n = 1/269); 1.72 in <1500 g (n = 1/579); 1.3 in <2500 g (n = 2/1588); and 0.41 in ≥2500 g (n = 1/2386 cases) birthweight, respectively).

The mean duration of hospitalization before onset of candidaemia (18.6 days; range, 0–90) was prolonged, and seven episodes (21.2%) occurred while children were receiving prophylactic or empiric antifungal therapy (Table 1). Malignancy including allogeneic HSCT (43.8%) and congenital malformations/syndromes (21.9%) were the most common underlying diseases; candidaemia in the context of sequelae of premature birth was infrequent (3.1%). The most frequent clinical characteristics associated with the occurrence of candidaemia were the use of broad-spectrum antibiotics at presentation (93.9%) or within the previous 2 weeks (69.7%), the presence of a central venous catheter (90.9%), and previous bacterial bloodstream infections (54.5%). *Candida albicans* was the most common species, accounting for 45.7%, followed by *C. parapsilosis* (17.1%) and *C. glabrata* (14.3%) (Table 2). There was no trend over time regarding the relative distributions of *C. albicans* and non-albicans *Candida* species. Non-albicans *Candida* species dominated in oncology/HSCT patients (60%; 9/15) and General Paediatric patients (64%; 7/11), whereas *C. albicans* was the predominant isolate in the remainder (60%; 6/9). None of the 32 isolates tested was resistant to all first-line antifungal agents, and resistance was virtually restricted to non-albicans *Candida* species. Antifungal therapy was initiated after a mean of 1.18 days (range, 0–5) following the acquisition of the first diagnostic blood culture. Antifungal monotherapy was administered in 23 episodes (fluconazole, seven episodes; liposomal amphotericin B, six episodes; caspofungin, three episodes; more than one agent sequentially, seven episodes) and combination therapy in ten episodes (30.3%). The mean duration of all antifungal therapy per episode was 25.5 days (range, 3–70). Most central venous catheters (80%, 24/30) were removed; the median time between the first diagnostic blood culture and the catheter removal was 5.66 days (range, 0–20).

TABLE 1. Demographic data and clinical characteristics of patients with candidaemia

Variable	Mean (range) or *n/x* (%)
Age (years)	7.50 (0–19)
Gender (male)	16 (50%)
Days of prior hospitalization	18.6 (0–90)
Prior antifungal therapy	7/33 (21.2)
Underlying disease	
Malignancy including allogeneic HSCT	14/32 (43.8)
Haematological malignancies	6
Paediatric solid tumours	5
s/p allogeneic HSCT	3[a]
Congenital malformations/syndromes	7/32 (21.9)
Cardiac malformations ± syndromes	3
Gastrochisis	1
Short bowel syndrome	1[a]
Complex retardation after premature birth	1[a]
Complex retardation plus syndrome	1
Metabolic disorders	4/32 (12.5)
Methylmalonic aciduria	3
Glutaric aciduria	1
Surgery, trauma, other acute conditions	4/32 (12.5)
s/p blunt abdominal trauma	1
s/p mastoidectomy	1
s/p appendectomy	1
Haemolytic uraemic syndrome with bowel perforation	1
Solid organ transplantation	2/32 (6.2)
s/p renal transplantation	2
Clinical characteristics[b]	
Neutropenia at presentation	10/33 (30.3)
Neutropenia in the last 2 weeks	8/33 (24.2)
Steroid use in the last 2 weeks	9/33 (27.3)
Immunosuppressive agents other than steroids	14/33 (42.4)
Mucositis at presentation	5/33 (15.2)
Graft-versus-host disease	2/33 (6.1)
Chemotherapy in the last 2 weeks	14/33 (42.4)
Abdominal surgery in the last 2 weeks	11/33 (33.3)
Total parenteral nutrition	7/33 (21.2)
Azotaemia at presentation	3/33 (9.1)
Dialysis at presentation	2/33 (6.1)
Central venous catheterization	30/33 (90.9)
Broad-spectrum antibiotics at presentation	31/33 (93.9)
Broad-spectrum antibiotics in the last 2 weeks	23/33 (69.7)
Bacterial BSIs in the last 2 weeks	18/33 (54.5)

BSI, bloodstream infection; HSCT, haematopoietic stem cell transplantation; s/p, *status post*.
[a]One patient had two episodes of candidaemia.
[b]Thirty-three evaluable episodes.

Severe sepsis or septic shock occurred in nine episodes (27.3%), and metastatic dissemination in five of the evaluable episodes (15.2%). Overall, four children (11.4%) died within 30 days of the first diagnostic blood culture; the 100-day mortality rate was the same. Three of the patients with a fatal course had a malignancy as underlying disease, accounting for a mortality rate in oncology/HSCT patients of 21.4% (not significant versus no malignancy/HSCT; chi-squared test). All four children who died had complicated candidaemia (severe sepsis/septic shock; dissemination) in comparison to six children (20.7%) among the survivors (p <0.005). The *Candida* species isolated in the four children who died included *C. albicans* (two children) and *C. lusitaniae* (two children).

This is the first study from Germany describing the current clinical and microbiological epidemiology of *Candida* bloodstream infections among an unselected population of hospitalized paediatric patients. With the exception of premature birth and low birthweight, underlying conditions and comorbidities were not different from those of other general paediatric series [4,5,7,8,16–18]. The pooled annual rate of candidaemia was 0.47 cases/1000 hospital discharges with higher rates in oncology/HSCT patients (1.25/1000), neonates (0.75/1000), ICU patients (0.59/1000) and cardiology patients (0.51/1000). These incidence rates are within those reported in adults [1] but are five-fold to more than ten-fold lower than those reported for paediatric patients from the

TABLE 2. Distribution of *Candida* isolates and resistance to antifungal agents

Candida species	No. (%) of episodes	No. of isolates tested	Antifungal agents and resistance breakpoints (mg/L)[a]						
			AMB >1	5-FC >16	FCZ >16	VCZ >2	CAS >2	AND >2	MCA >2
			No. of resistant isolates						
All	35 (100)	32	3	5	2	1	–	1	–
C. albicans	16 (45.7)	15	–	1	–	–	–	–	–
Non-*C. albicans*	19 (54.3)	17	3	4	2	1	–	1	–
C. parapsilosis	6	6	–	–	–	–	–	1	–
C. glabrata	5	4	1	2	1	1	–	–	–
C. lusitaniae	3	2	1	2	1	–	–	–	–
C. tropicalis	2	2	1	–	–	–	–	–	–
C. dubliniensis	1	1	–	–	–	–	–	–	–
C. pelliculosa	1	1	–	–	–	–	–	–	–
C. rugosa	1	1	–	–	–	–	–	–	–

AMB, amphotericin B; 5-FC, flucytosine; FCZ, fluconazole; VCZ, voriconazole; CAS, caspofungin; AND, anidulafungin; MCA, micafungin.
[a]Antifungal susceptibility testing was performed by the broth microdilution method according to DIN 58940-84 [13] with visual MIC reading after 48 h of incubation. Interpretive susceptibility breakpoints correspond to current CLSI recommendations [14,15] with the exception of FCZ [13]. Note that three strains could not be sub-cultured from their frozen stock culture and were therefore not available for *in vitro* susceptibility testing.

USA and Mediterranean countries, particularly for neonates [2,7,8,10,12]. The reasons for these differences are unknown but may be related to differences in socioeconomic features, rates of premature births, referral patterns, specialization and medical practices, as well as to design issues of the different surveys [1].

Similar to other general paediatric series [5,7,8,17,18], non-albicans *Candida* species accounted for the majority of isolates, with *C. albicans* and *C. parapsilosis* being the most frequent aetiological organisms. Resistance to approved first-line agents was limited to non-albicans *Candida* species, which is consistent with larger series that included from 120 to 200 *Candida* isolates [7,17,19]. Apart from a higher rate of primary combination therapy, the predominant use of amphotericin B and fluconazole in our study is in line with other contemporary reports [9,17] and reflective of the fact that newer agents were not approved in children at the time of the study. The majority of central venous catheters were removed with rate and timing being similar to those reported in other series [9,17,18]. Although the mean duration of all antifungal therapy per episode of 25 days was prolonged, this may indicate not only a severely ill patient population but also uncertainties about treatment endpoints.

The frequency of severe sepsis/septic shock (27.3%) was similar to reports in a systematic longitudinal study in adults with *Candida* bloodstream infections [20] and slightly lower than in paediatric patients with *Candida* sepsis mostly admitted to the ICU [18]. Dissemination to secondary sites (15.2% in our study) has been reported to occur in 10–20% of paediatric patients with candidaemia [4,9,21]. Prolonged fungaemia, use of vasopressors, immunosuppression including neutropenia, and prematurity have been identified as independent risk factors [4,9,21] and may be useful to identify patients in whom a specific screening is justified. The 30-day and 100-day mortality rates were 11.4% and at the lower end of the range of 10–25% reported in most general paediatric series [3,9,16,17,22]. Higher mortality rates close to 50% have been reported, predominantly in studies focusing on ICU patients [8,10,18]. Risk factors for mortality in paediatric patients with candidaemia include ICU admission [5,17], mechanical ventilation [16,17], hypotension or the presence of an arterial catheter [5] and neutropenia [16]. In contrast to adults [16,23] and similar to other paediatric reports [9,16], there was no apparent difference in mortality between *C. albicans* and non-albicans *Candida* bloodstream infections.

Transparency Declarations

AHG has served on the speaker's bureau and as a consultant to Astellas Pharma, Cephalon, Gilead Sciences, Merck & Co., Pfizer, Schering-Plough and Vicuron Pharmaceuticals. He has received research grants from Gilead Sciences and Merck & Co. WF has served on the speaker's bureau and as a consultant to Pfizer. He has received research grants from ICN Pharmaceuticals, MERLIN Diagnostika, Pfizer Pharma and Merck Sharp and Dohme. All other authors have nothing to declare.

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